

EXHIBIT 603.24

PLAINTIFFS' EXHIBITS 010582

Letter to the Editor

A Better Understanding of the Interpretation of Postmortem Blood Drug Concentrations*

To the Editor:

Since 1982, my research laboratory has been involved in the study of postmortem redistribution of drugs based both on an applied observational recording of medical examiner cases through the forensic toxicology laboratory at Hennepin County Medical Center as well as directing prospectively designed research investigations. Two issues that are recurrently confusing in the peer-reviewed literature as well as in the non-peer-reviewed press involve 1. how (forensic) toxicologists define postmortem redistribution and 2. the lack of detail in differentiating whether drug concentrations are reported as a "total" or "conjugated" concentration. The purpose of this editorial is to provide an evidence-based position on these two issues.

The topic of postmortem redistribution (PMR) has been extensively reviewed over the past several years (1–3). Several investigators have described multiple mechanisms that can be responsible for the release of tissue bound drugs from anatomic sites of high drug concentration to sites of lower concentration (concentration gradient); creating an artificially increased blood/fluid concentration postmortem that differs from the blood concentration that would have been present at the time of an individual's death. For drugs or classes of drugs that have been described in the literature which demonstrate increases in blood concentrations over a postmortem (PM) interval, the degree of confidence of the autopsy blood drug concentration as representative of the drug concentration that was present at the time of death (which could have been hours to days earlier) diminishes. The scientific fact is that PMR occurs in both in central (heart) blood as well as in peripheral (femoral) blood, as shown for numerous drugs in Table I. One of the most misstated definitions of PMR is based on the assumption that a PM heart blood (HB)-to-peripheral blood (PB) ratio greater than 1.0 is defined as PMR, and that the greater the HB/PB ratio, the greater the PMR. In reality, this ratio represents an anatomic site-to-site difference and may or may not be related to PMR (1–3). Whether or not the blood concentration of a drug observed at autopsy is the steady state concentration following stable, therapeutic dosing or represents an acute drug exposure resulting in death that has not appropriately distributed throughout the body, will have a substantial impact on the PM HB/PB ratio. What has been reported frequently is that central (heart) blood is more prone to PMR compared to peripheral blood and is related to the diffusion of drugs from the stomach, liver, lung, and heart tissues, tissues that often contain 2- to 10-fold greater drug concentrations than those found in blood (1–3,4). What has not been well studied is the extent of PMR in peripheral blood. However, there are numerous case reports and series of cases reported that clearly demonstrate that PMR does occur in peripheral blood (Table I) for the following drugs: citalopram (1,5), desethylamiodorone (6), dextropropoxyphene (7), digoxin (6,8), dothiepin (7), fentanyl (9–12), flecanide (13), haloperidol (14), MDMA/MDA (15), propoxyphene (16), solalol (6), thioridazine (14), and tricyclic antidepressants (16–18). An excellent overview of peripheral blood PMR addressing fentanyl was recently published by Palmer (12).

The general thought process has been that, because PMR occurs less frequently in PB compared to HB, PB drug



Table I. Published Studies Demonstrating Postmortem Distribution of Drugs

Drug	Blood Source	Reference Citation(s)
Citalopram	heart	1,5
Desethylamiodorone	heart, peripheral	6
Dextropropoxyphene	peripheral	7
Digoxin	heart, peripheral	6,8
Dothiepin	peripheral	7
Fentanyl	heart, peripheral	9–12
Flecainide	heart	6,13
Haloperidol	heart	14
MDMA/MDA	heart, peripheral	15
Propoxyphene	heart, peripheral	16
Solalol	heart, peripheral	6
Thioridazine	heart	14
Tricyclic antidepressants	heart, peripheral	16–18

* Disclosure: The author consults in medicolegal cases that involve drug concentrations in postmortem blood and tissue.

concentrations are a reliable indication of a drug concentration at the time of death. Using fentanyl as a representative case example (12), the biochemical and physical mechanisms responsible for increasing fentanyl concentrations in femoral/peripheral and heart blood over the postmortem interval are complex and likely vary from case to case. Fentanyl is a lipophilic drug, which is highly bound to proteins at physiological pH (7.4). A broad tissue uptake of fentanyl creates a large steady state volume of distribution. Fentanyl distribution can be described to occur in a three-compartment model: 1. the circulatory system (blood) plus vessel rich highly perfused tissue (liver, lung, heart) compartment; 2. peripheral compartment comprised of skeletal muscle; and 3. peripheral compartment comprised of adipose (fat) tissue. High partitioning of fentanyl into skeletal muscle occurs rapidly, with tissue concentrations 4- to 10-fold higher than in plasma (12). There is also a high tissue-to-blood concentration gradient for liver, 3- to 35-fold, and heart, 2- to 5.3-fold (11,18,19). Small decreases in plasma pH that can occur within minutes following death result in substantial decreases in protein binding of fentanyl. At death, there is a decrease in plasma pH, from the physiological pH of 7.4 in the living, to as low as 5.6 within 24 h postmortem. The pH decrease results in an increased permeability of tissue cell membranes, which results in a shift of drug concentrations to move along a concentration gradient (from the high tissue levels to the lower plasma levels). Postmortem fentanyl concentrations, both in the peripheral and central (heart) blood, may not stay static. When heart or peripheral blood is drawn it more likely than not does not reflect the blood concentration at the time of death, but reflects the combination of tissue-bound drug that has been released into the blood/fluid that is drawn at autopsy hours after death. I opine that this needs to be carefully considered in cause of death determinations when interpretation of PM drug concentrations is backed by literature in support of PMR. This is especially true in death cases in which blood concentrations may be overinterpreted as the cause of death based on the assumption that the peripheral PM blood concentration is an accurate record of the perimortem blood concentration at the time of death.

To assist the forensic toxicologist in interpretation of these difficult cases, some laboratories have moved to measuring PM tissue (liver) concentrations. The history of tricyclic antidepressant monitoring of liver levels, differentiating between fatal and therapeutic ingestions, has been established since 1970 (17,18,20). Recently, Anderson and Muto (21) have proposed the similar utilization of liver tissue to differential therapeutic from toxic or fatal fentanyl concentrations. The use of liver concentrations is further supported by the recent observations of fentanyl PMR in PB (11,12). Carefully designed studies need to be performed to better understand the relationship between central and peripheral blood and liver concentrations during the postmortem interval for drugs prone to PMR. Just as important are studies that have shown that, for some drugs, such as cocaine (22) and morphine (23), there was not a consistent and reproducible increase in drug concentration with the lapse of time (i.e., a temporal relationship). The studies did show that for several cases there were marked site-to-site differences in drug concentration, where the central blood concentrations were higher than in peripheral blood. These findings further underscore the fact that that a peripheral blood sample used to measure PM morphine or cocaine concentrations may not always approximate the perimortem blood concentration.

The second issue regards the lack of differentiating whether drug concentrations are reported as a "total" or "unconjugated" concentration in peer-reviewed literature. Because both medical examiners and coroners are often not appropriately trained in asking the right questions regarding toxicology laboratory analytical issues, such as 1. was the PM morphine concentration a total morphine (including both unconjugated and conjugated morphine) or was it an unconjugated morphine concentration, and 2. was the literature reviewed by the medical examiner to assist in correlating a PM blood morphine concentration and cause of death determination clear as to whether the reported morphine concentrations were unconjugated or total in the literature article used as a reference. For example, review of Baselt's section on morphine (24) does not adequately differentiate the studies that have reported total versus unconjugated concentrations. This could potentially mislead the interpretation by a medical examiner if they were to assume the blood level was a total concentration, yet reported as an unconjugated concentration that was possibly only 10 to 20% of the total concentration. Greater experimental detail needs to be forthcoming by all authors reporting unconjugated concentrations compared to total (unconjugated and conjugated) concentrations.

The overriding goal is to provide quality and dependable forensic toxicology results that can be reliably used for interpretation by all forensic scientists and pathologists (25). A better understanding of PMR of drugs and accurate reporting of unconjugated versus total drug concentrations, in both blood and tissue, will improve the field of forensic toxicology and better assist in the appropriate determination of cause of death investigations. Measurement of tissue (liver) concentrations instead of blood may be the insight needed to avoid the false increases in blood drug concentrations following PMR.

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Journal of Analytical Toxicology, Vol. 35, July/August 2011

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